Scanning Microscopy

Volume 7 | Number 1 Article 49

1-20-1993

Letter to the Editor by M.B. Engel and H.R. Catchpole Relating to: "Can We See Living Structures in the Cell" [by G.N. Ling, Scanning Microscopy Vol. 6, p. 405-450 (1992)] and Reply by G.N. Ling

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Scanning Microscopy, Vol. 7, No. 1, 1993 (Page 447-448) 0891-7035/93$5.00+.00
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Letter to the Editor by M.B. Engel and H.R. Catchpole relating to: "Can We See Living Structures in the Cell" [by G.N. Ling, Scanning Microscopy Vol. 6, p. 405-450 (1992)] and Reply by G.N. Ling

Dear Editor,

As workers in the field of ionic equilibrium in extracellular matrices and cells, and as contributors to this Journal of papers supporting an alternative explanation to that represented by the dominant schools of active transport (ionic pumps), we are surprised by the statement of Ling (1992, p. 449) which appears to limit published criticism of those schools to himself and A.S. Troshin. By an odd coincidence, our abstract (Catchpole *et al.*, 1951) on the distribution of potassium and sodium through selective action of the cations with ground substance and water appeared simultaneously with that of Ling (1951): "Tentative hypothesis for selective ionic accumulation in muscle cells". We have also published papers and monographs since that distant time. So much, at least, for longevity.

While agreeing that sodium pumps and all other energy-demanding ionic pumps are not the explanation of ionic distribution (e.g., with Cope and Hazlewood) (Joseph and Catchpole, 1978) and with Ling and Negendank (Catchpole, 1980), our approach has been different both theoretically and in experimental emphasis. Things that differ from the same thing are not necessarily identical.

The universal presence in cells of acidic and basic proteins and acidic DNA and RNA, and in extracellular matrix of highly acidic mucopolysaccharides led us to take fixed charge for granted and to treat all such species as having a net (negative) colloidal charge, which we were able to measure electrometrically, to estimate in several ways, and to quantitate more recently by microprobe (Engel and Catchpole, 1989).

We showed that the titration curves of muscle *in vivo* were strongly modified by the use of cations and anions (inductive effects), but were relatively insensitive to temperature change, and criticized the use of metabolic inhibitors as a highly dubious method of verifying the existence of ionic pumps driven by metabolism (Engel *et al.*, 1960).

As does Ling, we rejected the idea that cellular distribution of ions could be explained by a Donnan equilibrium based on the behavior of dilute solutions separated by a semipermeable membrane. Donnan (1924) himself cautioned against this. Yet it was the failure of cells to obey the Donnan membrane equilibrium that encouraged the suggestion of a sodium pump. As previously noted (Engel and Catchpole, 1989), pump hypotheses are based squarely on the failure of sodium and potassium ions to obey the wrong law.

Our treatment of ionic equilibrium (Joseph *et al.*, 1961, 1964, 1965; Joseph, 1973) adheres to the notation and equations of Gibb's heterogeneous equilibrium, and includes as essential elements: 1) net negative colloidal charge density, 2) ionic radii, hydration energies and standard chemical potentials of the ions, and 3) the dielectric properties of the dispersion medium (water).

We recognize that the theoretical treatment in this field is to some extent one of personal choice or taste, thus, for example, Ling's response to Rooman's question (Ling, 1992, p. 446) regarding the energy relations of potassium and sodium gradients. Joseph's paper (1973) on the efficiency of ion transport mechanisms answers this without reference to other hypotheses.

At the experimental level, Ling and co-workers have refuted the "proofs" of the pump hypotheses with admirable tenacity, and it is to be hoped that these will begin to vanish from the literature.

Our experimental work has been directed to the concept that cells and extracellular tissues are highly ordered structures made up of insoluble and soluble charged macromolecules and water. They are reversibly labile and subject to disaggregation, conformational change and entropic change (Catchpole and Joseph, 1973). The criterion for ionic equilibrium is that changes of chemical potential be constant for all ions of the same charge. In conjunction with known ionic values in cells and tissues, and without the need of adjunct hypotheses, we calculate values for the changes in standard chemical potentials of the physiologic ions (Na^+, K^+, Cl^-, Ca^{++}, Mg^{++}), resting potentials, and the dielectric constants of tissues such as muscle, tendon and cartilage. This, in brief, is our idea of a return to classical concepts which have been by-passed for half a century by the postulates of active transport.

Sincerely yours,

Jan. 20, 1993

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Reply by G.N. Ling

In 1981, Professor Hubert R. Catchpole wrote in the Perspectives in Biology and Medicine: "The first comprehensive review which mentioned the sodium pump in its title was that of Glynn and Karlish of 1975 (Ann. Rev. Physiol. 37-13, 1975)...Glynn and Karlish listed 245 articles in support of the sodium pump and none opposed. Yet Ling's idea had been around for 25 years; so had ours; so had Troshin's....".

In years following, I have often cited this passage to sound the alarm that serious violation of the basic ethics of science has become common place. For this and various other reasons, Drs. Joseph, Engel, and Catchpole (to be represented below as JEC) have always been my friends, as well witnessed by the fact that I acknowledged their friendship and constructive criticism in my most recent book, A Revolution in the Physiology of the Living Cell" (Krieger, Melbourne 1992).

It is thus entirely as their friends that I will answer their queries and hurt feelings that I had ignored to cite their work in my recent Scanning Microscopy (vol. 6, 1992) article "Can We See Living Structure in a Cell".

I begin by asking, Why should I have cited the work of JEC? The paper I wrote is, as the title indicates, on living structure in a cell. To the best of my knowledge, JEC have never written on the subject of living structure.

It is true that in presenting my view on the subject whether or not we can see living structure, I relied on the phenomenon of selective adsorption of K^+, Rb^+, Cs^+, Na^+ on the beta- and gamma-carboxyl groups of myosin in muscle cells. And JEC have also published on the subject of selective K^+ and Na^+ distribution in living cells. But their interpretation of selective accumulation is on the basis of differences in the thermodynamic "chemical potentials" of the different ions. A difference in chemical potentials does not tell us anything about mechanisms (see my answer to G.M. Roomans' question on page 446 of my Scanning Microscopy article) and the whereabouts the ions should be in the cell, whereas the whereabouts of K^+ and other ions plays a vital role in our argument. So why should I cite something that has no relevance to the subject of my paper? I cited Troshin and myself because we both presented our work on the subject of solute distribution in living cells earliest (in the year 1951). To the best of my knowledge, JEC did not publish their first paper on solute distribution in living cells, until ten years later in the Joseph *et al.* (1961) article mentioned above. (Selective distribution of K^+ and Na^+ on connective tissue ground substance, though relevant, is not the same as the selective distribution of K^+ and Na^+ in living cells).

There is hardly the need to point out that we live in an age of information deluge. Sometimes highly relevant references must be left out with reluctance. As it is, "Can We See Living Structure in a Cell" is already 45 (double-columned) pages long. JEC might well be facing a similar situation when writing their own paper, see e.g., Joseph *et al.* (1965) mentioned above. They made no reference to my work either, even though they did cite my **prior** work on selective K_+ and Na_+ distribution in their earlier 1961 article Joseph *et al.* (1961).

Finally I send to Drs. Joseph, Catchpole and Engel my greetings and hope I will meet them soon again, so that we can continue our discussion in person.

February 2, 1993 Gilbert N. Ling